Amendments to the Drawings:

The attached sheet of drawings includes changes to Figure 1. This sheet, which includes Figure 1, replaces the original sheet including Figure 1.

Attachment: Replacement Sheet and Annotated Sheet Showing Change(s).

REMARKS

Reconsideration of the present Application in view of the above amendments and the following remarks is respectfully requested. Claims 1-19 are currently pending. Applicants hereby cancel non-elected claims 6, 16-19 and claims 7 and 13 without acquiescence to any rejection and without prejudice to further prosecution of this subject matter in a related divisional, continuation, or continuation-in-part application. Applicants respectfully note that the Office Action Summary indicates with respect to Disposition of Claims that claims 6 and 15-19 are withdrawn from consideration and that claims 1-5 and 7-19 are rejected. As noted in the Action, Applicants elected Group 1b, claims 1-5 and 7-15, pursuant to a Restriction Requirement (Paper No. 6, November 18, 2002). Applicants therefore have assumed that the above-referenced Disposition of Claims contains a typographical error and that claims 1-5 and 7-15 are, in fact, currently under examination (Action, paragraph 3). Applicants have amended claims 1, 2, 8, and 9 and added new claims 20-32 to define more clearly embodiments of Applicants' invention. Support for the amended and new claims may be found in the specification, for example, at page 2, lines 16-18; page 3, lines 17-22; page 5, lines 1-10; page 6, line 6 through page 7, line 24; page 52, line 23 through page 56, line 4. No new matter has been added.

OBJECTION TO THE DRAWINGS

The drawing stands objected to under 37 C.F.R. § 1.84(p)(5) for allegedly failing to include on the drawing the reference "Figure 1" as referred to in the specification.

Applicants submit herewith a corrected drawing, which has been amended to include the reference notation "Figure 1." Applicants therefore respectfully submit that the drawings meet the formality requirements under 37 C.F.R. § 1.84 and request that the objection be withdrawn.

CLAIM OBJECTIONS

The Action objects to claims 7 and 13 for reciting non-elected material. The PTO requires correction.

Applicants respectfully submit that in view of the Amendment submitted herewith, which includes cancellation of claims 7 and 13 without acquiescence or prejudice, the objection is rendered moot.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1-5, 7, 14, and 15 stand rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. More specifically, the Action alleges that the specification fails to provide adequate guidance for a person skilled in the art to overcome without undue experimentation the unpredictability of applying results from *in vitro* experiments to regulating APP expression *in vivo* via ABC transporter expression. The Action cites several documents that allegedly exemplify the state of the art with respect to the nature and unpredictability of the invention and the breadth of the claims: (Lam et al., *J. Neurochem.* 76:1121-28 (2001); Schmitz et al., *J. Lipid Res.* 42:1513-20 (2001); Koldamova et al., *J. Biol. Chem.* 278:13244-56 (2003); Venkateswaran et al., *J. Biol. Chem.* 275:14700-707 (2000); Venkateswaran et al., *Proc. Natl. Acad. Sci. USA* 97:12097-102, (2002); and Schmitz and Kaminski, *Cell. Mol. Life Sci.* 59:1285-95 (2002)).

The Action also rejects claims 8-15 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. More specifically, the Action alleges that the specification fails to provide adequate guidance for a person skilled in the art to use small molecules to regulate the activity of ABC transporters that would regulate the expression of APP in a cell. The Action asserts that the specification does not provide adequate guidance to overcome the unpredictability of applying results from in vitro experiments to in vivo regulation of APP expression by regulating ABC transporter activity, which is allegedly exemplified in the documents cited above.

Applicants respectfully traverse these grounds for rejection and submit that as disclosed in the specification and recited in the instant claims, the claimed invention was fully enabled at the time the Application was filed. The invention is directed in pertinent part to a method for decreasing expression of amyloid precursor protein in a cell comprising contacting the cell with a small molecule that decreases expression or inhibits activity of an ABC

transporter, wherein decreasing expression or inhibiting activity of the ABC transporter thereby decreases expression of amyloid precursor protein, wherein the ABC transporter is an ABC transporter that is expressed in a brain cell.

Applicants submit that the instant specification provides sufficient guidance enabling a person skilled in the art to make and use the claimed methods for decreasing expression of amyloid precursor protein readily and without undue experimentation. The instant specification discloses that expression of amyloid precursor protein in a cell can be altered by modulating expression of a functionally active ABC transporter present in the cell. For example, the specification teaches that by increasing expression of an ABC transporter the level of amyloid precursor protein increases in the cell (*see, e.g.,* page 6, line 6 through page 7, line 10; Examples 1-3). Furthermore, in cells in which the function of an ABC transporter was inhibited, for example, by introducing mutations into the conserved Walker A or Walker B motifs (*see, e.g.*, page 65, lines 16-28; page 67, line 3 through page 68, line 4) thus decreasing the ability of the ABC transporter to act as an ATP-dependent pump, the expression of amyloid precursor protein was reduced compared with the level of expression of amyloid precursor protein in cells that also expressed a functionally active ABC transporter (*see* Examples 1-3). Accordingly, expression of amyloid precursor protein may be decreased either by effecting a decrease in expression of an ABC transporter or by inhibiting activity of the ABC transporter. As taught in the specification and recited in the instant claims, the ABC transporter is a transporter that is expressed in a brain cell (*see, e.g.,* page 7, lines 13-17). In one embodiment of the invention, the ABC transporter is ABCB6, ABCB9, ABCG1, ABCG4, ABCG2, ABCA1, ABCA2, ABCA3, ABCA5, ABCA6, ABCA8, ABCA9, ABCC5, ABCC10, ABCD1, ABCD2, or ABCD4. In certain embodiments, the ABC transporter is ABCB9, ABCG1, or ABCG4 (*see also* Examples 1-3).

Applicants respectfully point out that amyloid-β and amyloid precursor protein are not identical and that the present claims relate to a method for decreasing the expression of amyloid precursor protein and *not* to a method for decreasing amyloid-β expression as asserted in the Action (referring to Lam et al. (*J. Neurochem.* 76(4):1121-28 (2001) in paragraphs 12 and 24, pages 5 and 9, respectively). As described in the specification and understood in the art,

neuritic plaques that form during the development of Alzheimer's disease contain deposits of amyloid-β protein (*see, e.g.,* specification, page 1, lines 11-27; page 5, lines 2-20; Selkoe, *Nature* 399:A23-A31 (1999) (reference BO, form 1449 submitted May 14, 2002); Mills et al., *J. Neurosci.* 17:9415-22 (1997) (reference AL, form 1449 submitted May 14, 2002). Amyloid-β protein is a polypeptide derived by proteolysis of the amyloid precursor protein (*see id.*). Moreover, Lam et al. teach that cellular levels of amyloid precursor protein were increased in association with the increase in extracellular amyloid-β. Therefore, a person skilled in the art would predict by using the claimed methods for decreasing the level of amyloid precursor protein, the immediate precursor of amyloid-β, in a cell, a concomitant decrease in extracellular amyloid-β would be observed thus inhibiting or ameliorating amyloid plaque build-up (specification, page 7, lines 21-24; *see also, e.g.,* specification, page 62, lines 4-25).

Applicants submit that cell-based methods are predictive, useful, and accepted in the art for analyzing agents and methods effective for treating conditions and diseases related to amyloidosis such as Alzheimer's disease. Cell line models and animal chosen for particular studies should, as closely as possible, reflect or mimic a disease state or condition in a human in order to be useful for studying the pathology or treatment of the disease state or condition. Persons skilled in the art appreciate that animal cell culture models may be used to predict the efficacy of a method for treating a disease state associated with amyloidosis in humans. For example, the PC12 cell line is an art-accepted model for studying amyloid-β and amyloidosis, and treatments thereof (*see, e.g.*, Buxbaum et al., *Proc. Natl. Acad. Sci. USA* 87:6003-6006 (1990)).

Applicants respectfully disagree with the assertion in the Action that the state of the art of amyloid precursor protein is highly unpredictable and that the instant specification fails to provide adequate guidance for a person skilled in the art to make and use the claimed invention. Specifically, Applicants submit that the instant specification enables a person skilled in the art to practice the claimed methods using ABC transporters that are expressed in a brain cell (*e.g.*, ABCG1, ABCG2, and ABCG4) and disagree with the assertion in the Action that the scope of the claims is not enabled by the specification in view of Schmitz et al. (*J. Lipid Res.* 42:1513-20 (2001), cited at paragraphs 13 and 25 in the Action). While Schmitz et al. may not

"detail that [ABCG1 and ABCG4] have been found in the nervous system" (*see* Action, paragraph 13), Schmitz et al. do not state that the transporters are not expressed in nervous tissue. Schmitz et al. in fact indicate that ABCG1 is ubiquitously expressed, which would include expression in cells of the nervous system (Schmitz et al., Figure 1). Indeed, the state of the art supports that members of the ABCG subfamily of transporters are expressed in the nervous system. For example, Zhang et al. report that ABCG2 is expressed in brain endothelial cells and vessels (*FASEB J.* 17(14):2085-87 (2003)), and Annilo et al. describe that ABCG4 is highly expressed in the brain (*Cytogenet. Cell Genet.* 94:196-201 (2001)); (*see also* US-2003-0027259-A1).

Applicants also submit that the state of the art, for example Zhang et al. and Anillo et al. discussed above, also refutes the assertion in the Action (paragraphs 16 and 28) that the teachings in Schmitz and Kaminski (*Cell. Mol. Life Sci.* 59:1285-95 (2002)) confront a skilled artisan with a level of unpredictability that the ABCB9, ABCG4, or ABCG1 transporters are present in neuronal tissues and capable of affecting amyloid precursor protein expression. Applicants submit that the comment in Schmitz and Kaminski to which the Action points that "[u]nlike other ABC A-subfamily members, ABCA2 is predominantly expressed in the brain and neural tissues" (abstract) does not imply that other ABC A-subfamily members are not expressed in brain and neural tissues but that other subfamily members are not *predominantly* expressed in these tissues. In fact, Schmitz and Kaminski point out that ABCA2 was originally co-discovered with ABCA1 in 1994 from embryonic mouse brain (*see* page 1286, last full sentence, column 1). (See also Broccardo et al., *Biochim. Biophys. Acta* 1461:395-404 (1999), Figure 2, enclosed herewith.) Therefore, the state of the art supports the veracity of the disclosure in the instant specification, which provides enabling guidance for a skilled artisan to make and use the claimed methods.

The specification further teaches that a person skilled in the art may make and used the claimed methods for decreasing expression of amyloid precursor protein in a cell that expresses an ABC transporter by contacting the cell with any one of a number of compounds that are capable of modulating expression or activity of an ABC transporter. These compounds include a small molecule, which may be identified readily and without undue experimentation by

using routine screening methods. According to methods described in the specification and well known in the art, combinatorial libraries of small molecules may be synthesized (*e.g.*, page 53, line 15-20) and prepared for screening (*e.g.*, page 53, lines 21-27). By way of example, a list of suitable compounds is provided in the specification (page 54, line 22 through page 56, line 4 and references cited therein). Moreover, persons skilled in the art appreciate that assays which include screening a library of compounds can be performed by a variety of routine high throughput screening methods. (*See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (The test for enablement is not merely quantitative "since a considerable amount of experimentation is permissible.")).

Applicants respectfully disagree with the assertion in the Action that the specification provides insufficient guidance to a skilled artisan to make and use the claimed methods in view of Koldamova et al. (*J. Biol. Chem.* 278:13244-56 (2003)) (Action, paragraphs 14 and 26), Venkateswaren et al. (*J. Biol. Chem.* 275:14700-707 (2000)), and Venkateswaren et al. (*Proc. Natl. Acad. Sci. USA* 97:12097-12102 (2000)) (Action, paragraphs 15 and 27). While the documents teach that particular compounds, 22*R*-hydroxycholersterol and 9-*cis*-retinoic acid and oxysterols, induce or stimulate expression of ABCA1 (Koldamova et al. and Venkateswaren et al., *Proc. Natl. Acad. Sci. USA*) or ABCG1 (Venkateswaren et al., *J. Biol. Chem.*) via the liver X receptors (LXRs) and retinoid X receptors (RXRs), the documents fail to describe a relationship between expression of these transporters and expression of amyloid precursor protein. In contrast, as described in the instant specification, the claimed methods comprise contacting a cell with a small molecule that decreases expression of an ABC transporter, wherein decreasing expression of the ABC transporter thereby decreases expression of amyloid precursor protein in the cell.

Determination of the level of amyloid precursor protein or the level of an ABC transporter may be accomplished readily and without undue experimentation by a person skilled in the art using methods for detection of these polypeptides that are known in the art and described in the specification, such as immunological detection methods (*see, e.g.*, page 64, lines 23-29; page 66, line 27 through page 67, line 21, and references cited therein). A skilled artisan also can readily and without undue experimentation determine whether a compound when

contacted with an ABC transporter or a cell expressing an ABC transporter inhibits activity of the ABC transporter by using methods known in the art and described in the specification (*see, e.g.,* page 5, line 27 through page 6, line 4 and references cited therein; page 54, lines 2-21).

Accordingly, Applicants submit that the present specification fully enables the skilled artisan to make and use the claimed invention readily and without undue experimentation. Applicants therefore respectfully submit that the present application satisfies all the requirements of 35 U.S.C. § 112, first paragraph, and request that the rejections be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The Action rejects 1-5 and 7-15 under 35 U.S.C. § 112, first paragraph, asserting that the claims are directed to subject matter that is not adequately described in the specification. More specifically, the Action asserts that the claims are directed to a genus of small molecules that is defined by broad activities, regulating expression and/or activity of the large genus of ABC transporters, and that an insufficient number of small molecule species is described to show that Applicants were in possession of the invention at the time the instant application was filed.

Applicants respectfully traverse these grounds of rejection and submit that Applicants possessed the claimed invention, as disclosed in the present specification and recited in the instant claims, at the time the Application was filed. As described in the specification and recited in the instant claims, the invention relates to methods for decreasing expression of amyloid precursor protein in a cell by decreasing expression or inhibiting activity of an ABC transporter that is expressed in a brain cell. In one embodiment of the invention, the ABC transporter is ABCB6, ABCB9, ABCG1, ABCG4, ABCG2, ABCA1, ABCA2, ABCA3, ABCA5, ABCA6, ABCA8, ABCA9, ABCC5, ABCC10, ABCD1, ABCD2, or ABCD4 (*see, e.g.,* page 7, lines 13-17). Furthermore, the specification describes the relationship between the level of expression of an ABC transporter and the level of amyloid precursor protein in a cell by showing in working examples that increased expression of three different ABC transporters, ABCB9, ABCG1, and ABCG4, increased the level of amyloid precursor protein in the cell (Examples 1-3).

The specification further describes that decreasing expression of amyloid precursor protein may be accomplished by contacting an ABC transporter or contacting a cell that expresses an ABC transporter with a small molecule such that the activity or expression of the transporter is inhibited or decreased. Small molecules that decrease amyloid precursor protein expression may be readily obtained from any one of a number of combinatorial libraries (*see, e.g.,* specification, page 53, lines 3-27). The specification also describes suitable compounds that inhibit ABC transporters, thus providing numerous species within a genus of small molecules for use in the claimed methods (page 54, line 22 through page 56, line 4 and references cited therein; *see also* U.S. Patent No. 6,514,686, columns 14-15). Applicants submit that the structures of these molecules are known in the art and further submit that Applicants need not describe in detail in the specification what is conventional or known in the art.

In view of the above remarks, Applicants respectfully submit that the presently claimed subject matter is sufficiently described by the specification to reasonably convey to a person skilled in the art that Applicants possessed the claimed invention at the time the Application was filed. Applicants therefore submit that the instant Application complies with the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The PTO rejects claims 1, 7, 8, and 13 under 35 U.S.C. § 112, second paragraph, for indefiniteness. In particular, the Action asserts that the metes and bounds of the term "regulating" are unclear.

Applicants respectfully traverse this rejection and submit that the definition of "regulating" is sufficiently clear when read in light of the specification (*see, e.g.,* page 7, lines 18-24). Nevertheless, to point out even more particularly and to define more clearly the subject matter of the claimed invention and to expedite prosecution of the instant Application, Applicants have amended claims 1 and 8. The amended claims are directed in pertinent part to methods for decreasing expression of amyloid precursor protein in a cell comprising contacting

the cell with a small molecule that decreases expression or inhibits activity of an ABC transporter, wherein decreasing expression or inhibiting activity of the ABC transporter thereby decreases expression of amyloid precursor protein.

Applicants submit that rejection of claims 7 and 13 is rendered moot in view of the Amendments submitted herewith, which includes cancellation of these claims.

Accordingly, Applicants respectfully submit that the present claims meet the requirements for definiteness under 35 U.S.C. § 112, second paragraph, and request that rejection of these claims be withdrawn.

Claims 1-12 [*sic*] stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. In particular, the Action asserts that the claims are incomplete for omitting the essential steps of describing how ABC expression is regulated and what agents are used to perform this regulation.

Applicants respectfully traverse this rejection and submit that the basis for the rejection is obviated in view of the Amendments submitted herewith. Applicants submit that the present claims recite steps for practicing the claimed methods and recite compositions used in the claimed methods, thus satisfying the requirements for definiteness.

Applicants respectfully submit that all claims particularly point out and clearly define the subject matter of the invention as required under 35 U.S.C. § 112, second paragraph. Applicants therefore request that the rejection of these claims be withdrawn.

Applicants respectfully submit that all claims in the Application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned at (206) 622-4900.

Respectfully submitted,

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"Annotated Sheet Showing Change(s)"

Title: REGULATIC ; AMYLOID PRECURSOR PROTEIN EXPRESSION BY IFICATION OF ABC TRANSPORTER EXPRESSION OR ACTIVITY

Inventor(s): Peter B. Reiner et al. ~~Express Mail No. EL755731105US~~ Express Mail No. EV335467484 Docket No. 100103.402

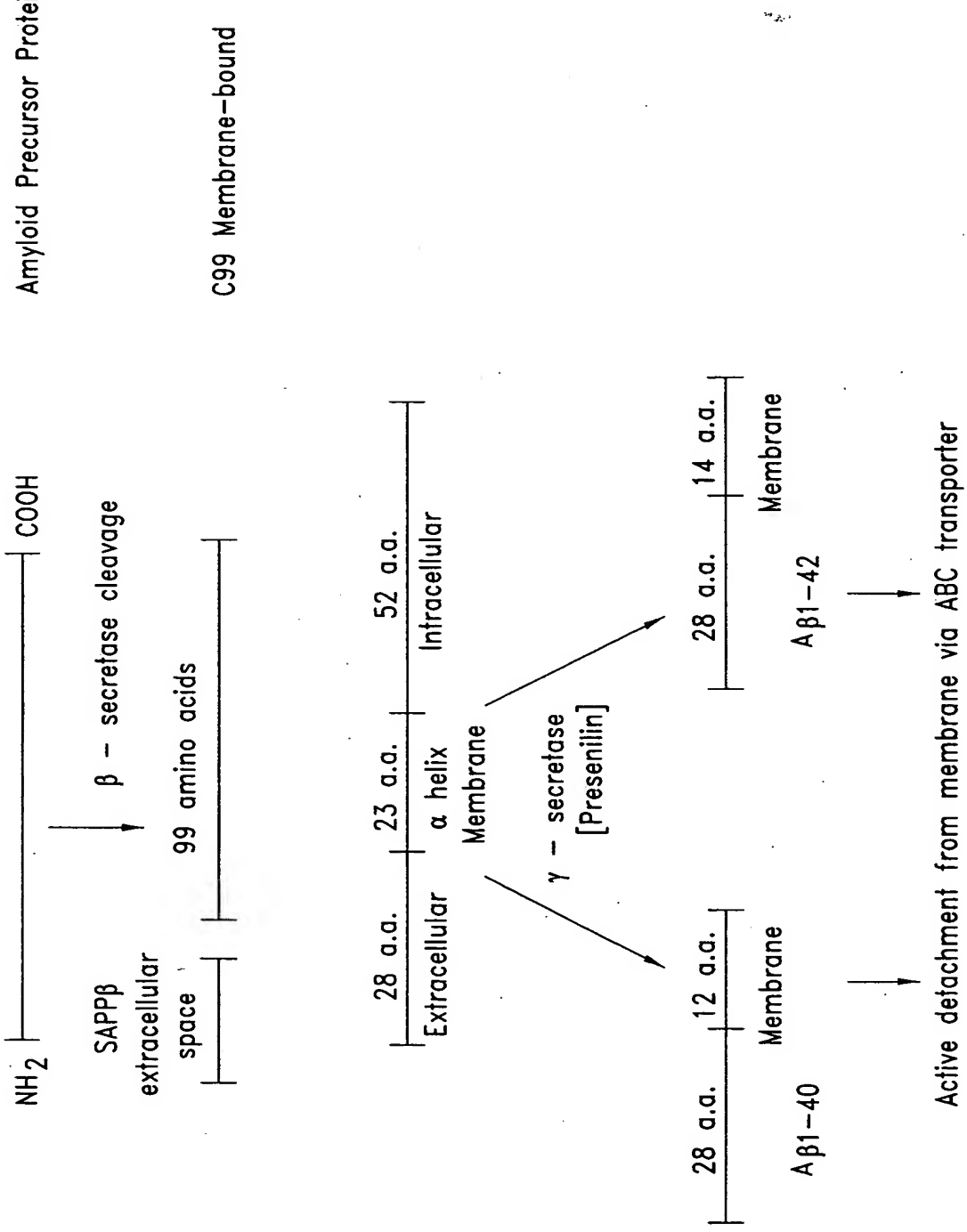

Figure 1